REMARKS

Applicant respectfully requests reconsideration. Claims 42-53, 59-69, 71-73 and 75-80 were previously pending in this application. No claim has been amended herein. No claim has been canceled. Claims 42-53, 59-69, 71-73 and 75-80 are still pending for examination with claims 42 and 71 being independent claims. No new matter has been added.

Rejection Under 35 U.S.C. 112

Claims 42-53, 59-69, 71-73 and 75-80 have been rejected under 35 U.S.C. 112, first paragraph, as lacking enablement.

The Office alleges that "the data provided by applicant does not directly support the broad claims" and that "Applicant has not shown a correlation of cancer specific immune response with the increase of these cytokines" (page 3 of the Office Action). Applicant respectfully disagrees and traverses the rejection. The data in the specification is sufficient to establish that certain cytokines are induced upon administration of unmethylated CpG oligonucleotides. At the time of filing this application, these cytokines were known to be useful in the treatment of cancer. Applicant respectfully submits that the data provided in the specification, coupled with the state of the art at the time of filing the application clearly establishes a reasonable correlation between the disclosed *in vitro* utility and the *in vivo* activity. Further, the Office has misunderstood the evidence submitted by Applicant. It is requested that the Office reconsider the evidence.

Applicant had previously cited several references (Trinchieri et al., Brunda et al., U.S. Pat. No.: 4,883,662, and Hayashi et al.) to describe the state of the art with respect to cytokine induction and the treatment of cancer prior to or around the priority date of the instant application. The purpose of the evidence was to show a correlation between the changes in immune function caused by CpG oligonucleotides and cancer. "Correlation" refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of use. The issue of "correlation" is dependent on the state of the prior art. MPEP § 2164.02. The Office repeatedly argues that that "[n]one of these references speak to the use of CpG oligonucleotides to treat cancer." Applicant respectfully submits that these references were not cited to demonstrate that prior to the invention

CpG ODNs were useful for treating cancer. Instead, the cited references are being presented to establish that at the time of filing the application, induction of certain cytokines was known to be useful in the treatment of cancer. Applicant's specification teaches that administration of CpG oligonucleotides induces these same cytokines. In view of the data in the specification and the state of the art at the time of filing the application as evidenced by the cited references, the skilled artisan would have expected that unmethylated CpG oligonucleotides are useful in the treatment of cancer.

The invention relates to the discovery that unmethylated CpG oligonucleotides can provoke an immune response, which includes the induction of interferon-γ (IFN-γ), IL-12, and IL-6, as well as NK cell activation (See *e.g.,* page 17, lines 3-8 of the application as filed). The references previous cited by Applicant (Trinchieri et al., Brunda et al., U.S. Pat. No.: 4,883,662, and Hayashi et al.) demonstrate that at the time of filing the application, there was an art-recognized connection between the induction of these cytokines and the treatment of cancer. For example, Trinchieri et al., Blood, V.84, December 15, 1994, specifically teaches that "studies using transplantable tumors in experimental animals have shown a dramatic affect of IL-12 in decreasing tumor growth and metastasis formation and in significantly delaying death.[134] Systemic Daily Treatment (5 days per week) had a significant inhibitory affect on the growth of metastasis induced by intravenous injection of B16 melanoma cells and efficiently inhibited the growth of subcutaneously injected tumors, even when treatment was initiated two weeks after tumor inoculation.[123] An inhibitory affect of IL-12 on tumor growth, with a greater than two-fold increase in survival of inoculated animals, was also observed with the reticulum cell sarcoma M5076 and with the renal cell adenocarcinoma renca.[134] In this latter tumor, complete remission, especially with peritumoral injection of IL-12, was observed in some animals; reinjection of the renca cells in the "cured" animals resulted in delayed growth of the tumor, suggesting that IL-12 may induce a memory immune response against the tumor.[134]" (Paragraph spanning 4021-4022).

Brunda et al. Journal Leukocyte Biology, V.55, February 1994 is a review article which also emphasizes the potent antimetastatic and antitumor activity of IL-12 that was observed in a number of murine tumor models. (P. 285, first column, last paragraph). U.S. Patent No. 4,883,662 issued on November 28, 1989, discloses an in vivo method for increasing NK cells in the blood of cancer patients because such NK cells have known activity against tumor cells (Abstract). Hayashi et al.,

Proceeding of the Japan Academy, Series B: Physical and Biological Sciences, 1994, 70, 205, teaches that cancer patients experiencing IFN-γ induction and/or strong skin reaction survived for longer periods of time than those patients showing no IFN-γ induction, who died after a short period. Accordingly, the cited references establish that the skilled artisan would have recognized the utility of a drug which is effective in inducing IL-12, IFN-γ and NK cell activation as a compound which would be useful in the treatment of cancer. The data presented in the specification demonstrate that unmethylated CpG oligonucleotides are effective in inducing these cytokines. Thus, Applicant has presented sufficient evidence to establish the correlation between the induction of the disclosed cytokines as well as NK cell activation and the treatment of cancer, and one of ordinary skill in the art would have recognized that unmethylated CpG oligonucleotides are useful in the treatment of cancer.

The Office also alleges that Krieg (J. Clin Invest. 117, 2007) teaches away from the use of CpG oligonucleotides as a monotherapy for the treatment of cancer" (Page 4 of the Office Action). Applicant respectfully disagrees. The claims are not limited to monotherapy. The addition of other therapeutic agents is encompassed by the broadest claims. Further claims 43, 44, 68, 72-73, and 79-80 all specifically recite the combination of a CpG ODN with a second therapeutic agent. Further, the overall teachings of Krieg (2007) support the therapeutic value of CpG oligonucleotides in the treatment of diseases such as cancer. Krieg teaches that "In mice with relatively small tumors, up to a few millimeters in diameter, CpG monotherapy can be sufficient to induce T cell-mediated tumor regression", and "In human also, monotherapy with the TLR9 agonist CPG 7909 (now called PF-3512676 when used in oncology without a vaccine) or another B-class CpG ODN, 1018 ISS, activates NK cells and induces a Th1 cytokine response in humans with B cell lymphomas." (Page 1190, first column, last paragraph). Table 2 and Table 3 provides a list of published and ongoing clinical trials, including phase I and phase II monotherapy using CpG oligonucleotides. When read in its entirety Krieg is supportive of the claimed invention.

In conclusion, Applicant has met the enablement standard by teaching the skilled artisan how to make and use the claimed invention without undue experimentation based on the teachings provided in the specification and based on the knowledge in the art at the time of filing of

the application. The Office has not provided sufficient evidence to establish a lack of enablement of the claimed methods.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. C1039.70021US01.

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Respectfully submitted,

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